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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,429	01/22/2002	Ekambar R. Kandimalla	47508-580 (HYZ-027CIP)	7279

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,429	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-20* is/are pending in the application.

4a) Of the above claim(s) *6,7,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,8-13 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Double Patenting

2. Claims 18-19 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15-22 of U.S. Patent No. 6,372,427 B1, for the reasons of record set forth in the Office Action mailed 4-20-2004.

3. Applicant's arguments filed 10-22-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the instant rejection is improper because the claims do not provide every element of the claimed invention. According to Applicants the examiner improperly references the specification as support for the rejection, however the specification is to be used only as a dictionary in determining the meaning of terms of the claimed invention.

Contrary to Applicant's assertions, the MPEP refers to two exceptions to the general prohibition of using the disclosure of a potentially conflicting patent or application in an ODP-Obviousness analysis. The two exceptions are:

1. The disclosure can be used as a dictionary for claim terminology; and

2. "[T]hose portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent" (MPEP § 804).

The MPEP further notes:

The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103 since only the disclosure of the invention claimed in the patent may be examined."

Therefore, referencing the disclosure to identify obvious variations of the claimed invention is permitted as per MPEP § 804.

Additionally, Applicants argue that the portions of the specification cited by the Examiner in the instant rejection as supporting "compositions" comprising the synthetic oligonucleotides of the invention do not render obvious a "pharmaceutically acceptable carrier." First, it is noted that Applicants have currently amended the instant claims to include a "pharmaceutically acceptable carrier." This newly added limitation is also an obvious variation of the claimed invention, since the disclosure of this issued US Patent clearly states: "[t]he synthetic oligonucleotides of the invention may be used as a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of

administration. Such a composition may contain, in addition to the synthetic oligonucleotide and carrier, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art." (col. 13-14, bridging ¶)

Absent evidence to the contrary, the claims of the issued US Patent represent an obvious alternative embodiment of the instantly claimed invention recited in claims 18-19, and are therefore unpatentable.

Claim Rejections - 35 USC § 103

4. Claims 1-3, 5, 8-13, and 17 remain rejected, and claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gryaznov et al. (US Patent No. 5,571,903) in view of Agrawal et al. (US Patent No. 5,691,316), for the reasons of record set forth in the Official Action mailed 4-20-04. (Claim 6 was improperly included in the instant rejection in the Office Action mailed 4-20-04, claim 6 is a non-elected claim).

5. Applicant's arguments filed 10-22-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the '903 patent describes complexes that form only after the individual oligonucleotides have annealed to their targets utilizing non-specific, low affinity interacting moieties such as lipophilic groups. In contrast, Applicants assert that the instant invention requires the presence of a pair of highly specific, high affinity binding partners which enable the oligonucleotide to form a complex independent of, and prior to, annealing to target nucleic acid.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the presence of a pair of highly specific, high affinity binding partners which enable the oligonucleotide to

form a complex independent of, and prior to, annealing to target nucleic acid) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Additionally, Applicants argue that the 903' does not provide for the specific formation of heterodimeric cooperative oligonucleotides that can productively bind to adjacent tandem portions of a target mRNA while avoiding the formation of homodimeric complexes that cannot bind adjacently to the target mRNA. Again, the instant claims do not require the formation of the heterodimeric cooperative oligonucleotides mentioned by Applicants. Applicants are relying upon limitations that are not recited in the instant claims to distinguish the instant invention from the prior art.

Moreover, Applicants argue that the '316 patent does not teach the covalent attachment of cyclodextrin to an oligonucleotide, which is a critical feature of one of the embodiments of the instant invention. However, again as stated above, the instant claims do not require the covalent attachment of cyclodextrin to either of the first or second synthetic oligonucleotides of the claimed invention. Again, Applicants are relying upon limitations that are not recited in the instant claims to distinguish the instant invention from the prior art.

Applicant's arguments do not take the place of evidence. It remains that it would have been obvious at the time the instant invention was made to modify the oligonucleotides of Gryaznov et al. with the cyclodextrin or adamantine / cyclodextrin modifications of Agrawal et al. in the design of the presently claimed invention. One of ordinary skill in the art would have been motivated to make this modification because the cyclodextrin or adamantine/cyclodextrin

modifications are known in the prior to increase the cellular uptake of oligonucleotides comprising these modifications and thereby increase the efficacy of their application and reducing the dose required (see Agrawal et al. col. 5, lines 11-17).

Newly added claim 20 recites the composition of claim 3, comprising a synthetic linkage selected from the group consisting of alkylphosphonates, phosphorothioates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, phosphoramidites, carbamates, carbonates, phosphate esters, acetamidate, and carboxymethyl esters. Agrawal et al. teach that preferable synthetic linkages include alkylphosphonates, phosphate esters, phosphorothioates, phosphorodithioates, carbamates, and alkylphosphonothioates (see bridging ¶ of col. 2-3). Therefore, the invention recited in instant claim 20 is also rendered obvious by the disclosures of Gryaznov et al. in view of Agrawal et al.

Claim Rejections - 35 USC § 112

6. Claims 9-10, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 9-10 recite the limitation "duplex structure" in the first line. There is insufficient antecedent basis for this limitation in the claim. Claims 9-10 depend from claim 8, which recites the phrase “dimeric structure,” and does recite the phrase “duplex structure.”

8. Newly added claim 20 recites the composition of claim 3, comprising a synthetic linkage selected from the group consisting of alkylphosphonates, phosphorothioates, phosphorodithioates, phosphate esters, alkylphosphonothioates, phosphoramidates, phosphoramidites, carbamates, carbonates, phosphate esters, acetamidate, and carboxymethyl

esters. It is noted that the terms "phosphoramidates" and "phosphate esters" are repeated in the recited group.

9. Claims 16-19 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the claimed pharmaceutical formulations and compositions *in vitro*, does not reasonably provide enablement for the *in vivo* use of the claimed formulations or compositions for treatment purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth in the prior Office Action.

10. Applicant's arguments filed 10-22-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that instant rejection relies upon quotations from references that address concerns associated with the use of monomolecular antisense pharmaceuticals. Moreover, Applicants traverse the instant rejection by citing numerous instances of successful *in vivo* therapeutic applications. Applicants argue that the conjectural concern over non-antisense effects is not at all determinative to enablement of the instantly claimed invention. Moreover, according to Applicants "[M]uch of the 'unpredictability' cited in the Office Action pertains to target accessibility and other factors that have already been worked out in these numerous examples where an effective antisense therapeutic has been developed."

Contrary to Applicant's assertions, Applicant's allegation of complete enablement for the full breadth of compounds encompassed by the instant claims is not supported by the specification as filed. Applicants argue that the supporting references cited in this rejection

addressed only the use of monomeric antisense oligonucleotides and are not directly relevant to the instant invention. However, it is noted that the enablement of the instant invention is further complicated by the need to deliver multiple oligonucleotides to a single target within a cell. Applicants do not provide any specific guidance regarding the delivery of the instant compounds. Although Applicants cite multiple cases of *in vivo* antisense therapy, these references can also be considered not directly relevant to the instant invention which requires the use of multiple tandem, non-overlapping oligonucleotides to a single target nucleic acid, for a sufficient time, and at a sufficient concentration, to inhibit a single target nucleic acid to such an extent that a therapeutic result is produced. Applicants have not provided any specific guidance in this regard. The instant specification has an effective filing date of 4/12/1995, at that particular time the Examiner is unaware of successful *in vivo* antisense therapeutics available at that time. As stated in the prior Office Action, as of the year 2000, according to Jen et al. (*Stem Cells,* Vol. 18: 307-319, 2000) many challenges remained that precluded antisense-based therapy from becoming routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[G]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[A] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (see page 315, last two paragraphs).

Moreover, although Applicants make reference to successful *in vivo* applications of antisense based therapeutics, Applicants have not provided any evidence that the guidance

provided in these successful treatments were known in the art as of the filing date of the instant invention. To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing (See MPEP 2164.05(a)). In one particular instance, Applicants refer to the use of 2nd generation antisense compounds used to achieve successful *in vivo* treatments, however it is noted that Applicants reference Zheng (1999). It is noted that the instant specification, has an effective filing date of 4/12/1995. Applicant's specification makes no mention of the 2nd generation antisense compounds used in Zheng (1999).

Applicant's arguments do not take the place of evidence. As stated in the prior Office Action, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the behavior of oligonucleotides *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a mRNA target, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a complex of multiple oligonucleotides is delivered to a particular site, and a single nucleic acid target is inhibited and the desired treatment effects are obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
Art Unit 1635

JLE